Donepezil therapy enhances endothelium-dependent and endothelium-independent cutaneous vasodilation in Alzheimer's disease patients.

Jonathan Maltz[1], Jamie Eberling[1], William Jagust[2], Thomas Budinger[1]
[1]Lawrence Berkeley National Laboratory, University of California, Berkeley, CA, United States; [2]University of California, Davis, CA, United States

Summmary

We have observed an enhanced dilatory response to the application of methacholine (MCh), acetylcholine (ACh) and sodium nitroprusside (SNP) in Alzheimer's disease (AD) subjects under donepezil (Aricept) therapy.

Previous studies have observed preserved (Hornqvist et al. 1987) or impaired (Algotsson et al. 1995) vascular response to cholinergic agonists in medication-naive AD patients.

We believe that the enhanced response is due in part to the impairment of the metabolism of cholinergic agonists by the acetylcholinesterase inhibitor (AChEi) donepezil.

The well-tolerated non-invasive method used to evaluate vascular response may provide a useful peripheral surrogate marker for assessing responsiveness to AChEi therapy, and for dose titration purposes.

Review of previous work

Three studies have investigated cutaneous vasoactivity in AD:

Hornqvist et al. used iontophoresis and a semi-quantitative visual evaluation of perfusion response and found the following differences between the AD and control groups:

Hörnqvist et al.: Perfusion response results

Agent	Action	AD vs Control
Phenylephrine	α_1-agonist	AD slightly reduced
Isoproterenol	β_1-agonist	AD reduced $p < 0.001$
Methacholine	Muscarinic agonist	Not significant

Hörnqvist et al., Gerontology 33(6), 1987

Hörnqvist et al.: Subject selection

12 AD/SDAT patients
Age: 52-84, mean 71
Severe dementia, hospitalized

13 controls with various dermatoses
Age: 52-82, mean 70

Nicotine and caffeine allowed

In 1995 Algotsson et al. employed iontophoresis and laser Doppler imaging, and observed decreased response to β_1-agonist isoproterenol and cholinergic agonist ACh in AD subjects.

Algotsson et al. 1995.: Perfusion response results

Agent	Action	AD vs Control
Sodium nitroprusside	NO donor to smooth muscle	AD reduced (not significant)
Isoproterenol	β_1-agonist	AD reduced $p < 0.01$
Acetylcholine	Endothelium dependent vasodilator	AD reduced $p < 0.05$

Algotsson et al., Neurobiology of Aging 16(4), 1995

Algotsson et al.1995: Subject selection

15 AD patients
Mini-mental state examination (MMSE) > 27
16 Age-matched controls
Subjects lived at home

In 2000 Algotsson et al. employed iontophoresis and laser Doppler imaging, and hypothesized that an observed increased response to sodium nitroprusside amongst AD patients harboring the Apolipoprotein E ε4 allele (ApoE4) stemmed from greater sensitivity to iontophoretic current in this patient group.

Algotsson et al. 2000: Perfusion response results

	Patients with ApoE4	Patients without ApoE4	Controls
	on AChEi: 4	on AChEi: 1	
Sodium nitroprusside	Significantly enhanced	Normal	Normal
Acetylcholine	Not significant	Not significant	Not significant
Isoprenaline	Not significant	Not significant	Not significant

Algotsson et al., Arch. Gerontol. Geriatr. 31 (2000) 221-231

Algotsson et al. 2000: Subject selection

9 AD patients with ApoE4, 4 of whom on AChEi
8 AD patients without ApoE4, 1 of whom on AChEi
11 Controls, 1 of whom with ApoE4
All non-smokers

Methods

Vascular responses to methacholine chloride (MCh), acetylcholine chloride (ACh) and sodium nitroprusside (SNP) were evaluated in AD subjects and age-matched controls.

These chemicals were applied in controlled doses using iontophoresis. The ensuing cutaneous vascular response was assessed by means of laser Doppler perfusion imaging.

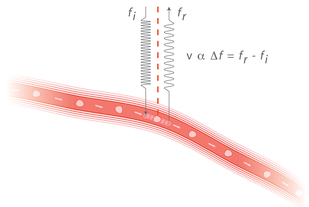

Figure 1. Laser Doppler imaging of red blood cell velocity.

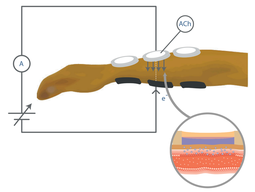

Figure 2. Iontophoresis of ACh.

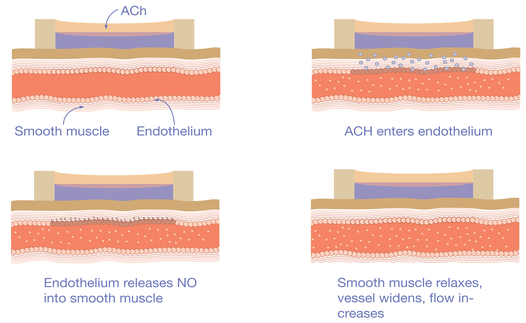

Figure 3. Vessel dilation in response to iontophoresis of ACh.

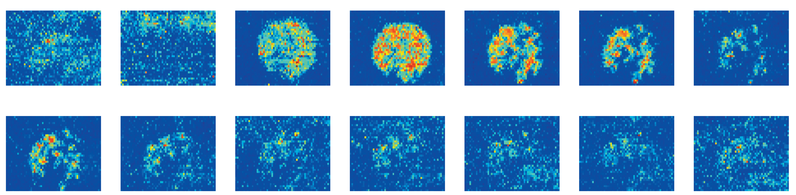

Figure 4. Laser Doppler perfusion imaging of typical cutaneous vasoactivy in response to iontophoresis of ACh.

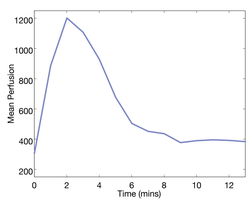

Figure 5. Typical perfusion response to iontophoresis of ACh.

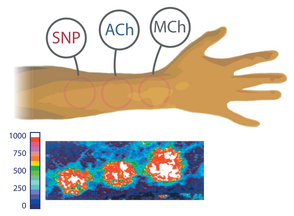

Figure 6. Laser Doppler imaging of perfusion response to iontophoresis of SNP, ACh, MCh.

Results

Cutaneous vascular perfusion responses to SNP, ACh and MCh were significantly increased in the AD group under donepezil therapy:

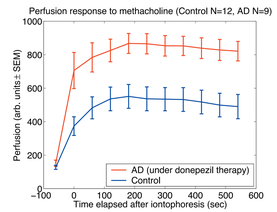

Figure 7. The area under the MCh perfusion vs. time curve (AUC) is increased 78% in the medicated AD group.

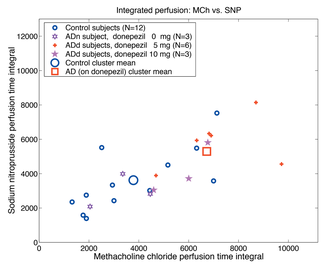

Figure 8. Scatterplot showing AUC for MCh vs. AUC for SNP for all subjects and corresponding group means. The three unmedicated AD subjects' responses do not differ significantly from those of the controls.

Perfusion response results

Agent	Unmedicated AD vs Control	AD on donepezil vs Control
Sodium nitroprusside	Not significant	AD enhanced 46%, $p < 0.05$
Acetylcholine	Not significant	AD enhanced 68%, $p < 0.03$
Methacholine	Not significant	AD enhanced 78%, $p < 0.003$

Subject selection

9 AD patients on donepezil
Age: 73-88, mean 80
MMSE: 2 - 28, mean 19

3 unmedicated AD patients
Age: 64-83, mean 73
MMSE: 20 - 29, mean 24

12 controls
Age: 69-84, mean 77

Subjects fasted and abstained from nicotine for 12 hours before the study.

We investigated whether the vascular response was correlated to the donepezil dose:

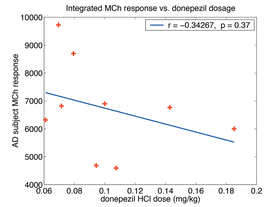

Figure 9.

No significant linear correlation could be found. An "inverted-U" dose-response characteristic has been observed among some AChEi's (Sramek and Cutler, Alz. Dis. Assoc. Disord. 2000; 14:216-27). More data will be needed for fitting and validation of such a model.

The results of this study may provide an alternative explanation for the enhanced response observed by Algotsson et al. in ApoE4 AD subjects: 44% of ApoE4 AD subjects were under AChEi therapy; 13% of non-ApoE4 AD subjects were under AChEi therapy .

Acknowledgements

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